

form understood by those skilled in the art to mean that particles are capable of passing through a mesh of "X" but not capable of passing through a mesh of larger than "Y". In the absence of the language X to Y mesh meaning this (as Applicant has elaborated on in the December 8, 2005 Amendment), the upper range (the "Y" value) would be meaningless. That is, if the inclusion of the upper mesh value does not eliminate particles capable of passing therethrough, it would not have to be stated.¹

Still further, to describe a particle as passing through a mesh of "X", inherently means that a range of particle sizes passes therethrough, unless the particle size is expressly described to be the same. Applicant has not described, or inferred, that the particle size is the same anywhere in its specification.

As evidence of this common usage of this language (precisely as used by the Applicant), Applicant is enclosing herewith several articles. The articles each bear the web site identification on the top thereof.

Attachment A uses the language "X to Y mesh" as used by the Applicant. As can be seen, the different mesh ranges separate a range of different particle sizes. The smaller mesh numbers, which account for larger opening sizes, produce a larger average particle size.

Similar language is used in Attachments B, C and D.

Attachment E uses similar terminology but uses a slight variation of this convention; "X/Y mesh" versus "X to Y mesh". However, as explained on the cover page of

¹ This explanation is further supported by the description in Applicant's specification, on pages 16-18.

Attachment E, and as highlighted thereon, 32/42-mesh defines a material size that passes through 32 mesh but is trapped in a 42 mesh sieve.

It is respectfully submitted that the terminology that Applicant has used since the original filing of its application is conventionally known to mean that a mesh of "X to Y" includes a range of particle size capable of passing through a mesh of X but not capable of passing through a mesh larger than Y. Accordingly, the language added in the December 8, 2005 Amendment is fully supported by the original disclosure.

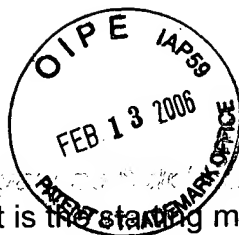
With this clarification, it is believed that all pending claims are in allowable form. Entry of the December 8, 2005 amendment and allowance of the case are requested.

Respectfully submitted,

By 
John S. Mortimer, Reg. No. 30,407

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Date: Feb 8, 2006

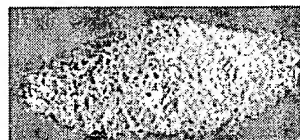


Products Introduction

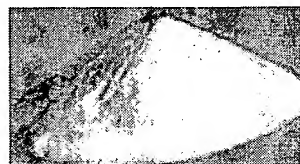
Uses: It is the starting material for electrolytic manganese metal, electrolytic manganese dioxide, fungicide and other manganese compounds including manganese carbonate, manganese salt for drying and inorganic pigments. It is also used in textile printing and glass making. Very significant in terms of volume, it is used as fertilizer for manganese-deficient soil and additive for animal feeds.

Specifications:

Purity($\text{MnSO}_4 \cdot \text{H}_2\text{O}$):	98%min.
Manganese(Mn):	31.8%min.
Iron(Fe):	0.004%max.
Chloride(Cl):	0.004%max.
Water insoluble:	0.05%max.
Heavy metal(Pb):	0.0015%max.
Arsenic(As):	0.0005%max.
PH value:	5-7



6-10 mesh



powder

Sizes: (powder) 60-100 mesh;
(granular) 6-10 mesh or 10-50 mesh.

Packing:

Net Weight: 25, 50kgs P.P. woven bag with pe liner; or 1000 kgs big bags

2. Zinc Sulphate(ZnSO_4)

Uses: It is used as raw material for production of lithopone. It is also used in synthetic fiber industry, zinc plating, pesticides. It is mainly used in trace element fertilizer and feed additive, etc.

Specifications:

(1) Zinc Sulphate Monohydrate($\text{ZnSO}_4 \cdot \text{H}_2\text{O}$):

Purity($\text{ZnSO}_4 \cdot \text{H}_2\text{O}$):	98%min.
Zinc(Zn):	35%min.
Water insoluble:	0.05%max.
Heavy metal(Pb):	0.0015%max.
Arsenic(As):	0.0005%max.
PH value:	5-7



10-20 mesh



powder

Sizes: (powder) 60-100 mesh;
(granular) 6-10 mesh or 10-50 mesh.

Attachment A

1/2

Packing:

Net Weight:25,50kgs P.P. woven bag with pe innerbag;or 1000 kgs big bags.

(2)Zinc Sulphate Heptahydrate($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$):

Purity($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$):	98%min.
Zinc(Zn):	22%min.
Water insoluble:	0.05%max.
Heavy metal(Pb):	0.002%max.
Arsenic(As):	0.001%max.
Cadmium(Cd):	0.002%max.

Sulfur Dioxide(SO2)(Gaseous)

Uses: It is mainly used as bleaching agent for processing leathers,fabric and organic matter,medium colouring agent for printing and dyeing;germicide and antiseptic for food preserving,brewing and beverage. It is also used as auxiliary material for synthetic dyes,perfume and photographic fixing agent,etc.

Specifications:

Main content(SO_2):	65%min.
Iron(Fe):	0.005%max.
Water insoluble:	0.05%max.
Heavy metal(Pb):	0.002%max.
Arsenic(As):	0.0002%max.
PH value:	4.5-5.5



powder

Packing:

Net Weight:25,50kgs P.P. woven bag with pe liner;or 1000 kgs big bags.

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 - Salts and Oxides
 - Solvents
 - Titration
- + Key Resources
- + MedBasics
- + Key Resources

Adsorbents

LabBasics - EU

Product Name	Product #
Activated charcoal purum granulated	18002
Activated charcoal granular Pore Size 20-40 mesh	242268
Activated charcoal granular Pore Size 4-12 mesh	242233
Activated charcoal powder Pore Size -100 mesh	242276
Activated charcoal pore volume ~1.5 cm ³ /g (dry basis)	278092
Activated charcoal decolorizing	161551
Activated charcoal	329428
Aluminum oxide standard grade Pore Size ~150 mesh Pore Size 58 Å	199966
Aluminum oxide standard grade Pore Size ~150 mesh Pore Size 58 Å	199974
Aluminum oxide standard grade Pore Size 58 Å Pore Size ~150 mesh Pore Size 58 Å	199443
Aluminum oxide powder Particle size 10 µm 99.7 %	265497
Ascarite® Sodium hydroxide-coated silica. Pore Size 8-20 mesh	223913
Ascarite® Sodium hydroxide-coated silica. Sodium hydroxide-coated silica. Pore Size 20-30 mesh	223921
Calcium sulfate with indicator Pore Size 4 mesh	238961
Calcium sulfate with indicator Pore Size 6 mesh	456071
Calcium sulfate with indicator Pore Size 8 mesh	238988
Calcium sulfate without indicator Pore Size 4 mesh	238910
Calcium sulfate without indicator Pore Size 6 mesh	238929
Calcium sulfate without indicator Pore Size 8 mesh	238937
Diatomaceous earth	392545
Filter agent, Celite®	167436
Filter agent, Celite® 521	221791
Filter agent, Celite® 545	419931
Filter agent, Celpure® P100	526266
Filter agent, Celpure® P1000	525227
Filter agent, Celpure® P300	525243
Filter agent, Celpure® P65	525235
Florisil® particle size 30-60 mesh	288691
Florisil® particle size 60-100 mesh	220744
Florisil® reagent grade particle size 60-100 mesh	220752
Florisil® particle size 100-200 mesh	220736
Florisil® Pore Size -200 mesh	288705
Molecular sieves beads Pore Size 4-8 mesh	208574
Molecular sieves beads Pore Size 4-8 mesh	208590
Molecular sieves beads Pore Size 4-8 mesh	208639
Molecular sieves beads Pore Size 8-12 mesh	208582
Molecular sieves 4A beads Pore Size 8-12 mesh	208604
Molecular sieves beads Pore Size 8-12 mesh	208647
Molecular sieves pellets Particle size 1.6 mm	334286
Molecular sieves pellets Particle size 1.6 mm	334308
Molecular sieves pellets Particle size 3.2 mm	334278
Molecular sieves pellets Particle size 3.2 mm	334294
Molecular sieves powder Particle size 5 µm	233668
Molecular sieves, 5Å beads Pore Size 4-8 mesh	208612
Molecular sieves, 5Å beads Pore Size 8-12 mesh	208620

Attachment B 1/2

Sand Pore Size -50-+70 mesh	274739
Silica gel ACS reagent	336815
Silica gel Davisil™ Pore Size 60 Å pore volume 0.75 cm ³ /g 99 %	236756
Silica gel Davisil™ Pore Size 60 Å pore volume 0.75 cm ³ /g 99+ % particle size 200-425 mesh	236772
Silica gel Davisil™ Pore Size 60 Å pore volume 0.75 cm ³ /g 99+ % particle size 100-200 mesh	236780
Silica gel Davisil™ Pore Size 60 Å pore volume 0.75 cm ³ /g 99+ %	236799
Silica gel Davisil™ Pore Size 60 Å pore volume 0.75 cm ³ /g 99+ % particle size 35-60 mesh	236802
Silica gel Davisil™ Pore Size 150 Å pore volume 1.15 cm ³ /g 99+ % particle size 200-425 mesh	236810
Silica gel Davisil™ 99+ % Pore Size 150 Å pore volume 1.15 cm ³ /g particle size 100-200 mesh	236829
Silica gel Davisil™ Pore Size 150 Å pore volume 1.15 cm ³ /g 99+ % particle size 60-100 mesh	236837
Silica gel 99+ % Pore Size 150 Å pore volume 1.15 cm ³ /g Davisil™ particle size 35-60 mesh	236845
Silica gel Merck™ Pore Size 60 Å particle size 230-400 mesh	227196
Silica gel Merck™ Pore Size 40 Å pore volume 0.68 cm ³ /g particle size 35-70 mesh	242179
Silica gel Merck™ Pore Size 60 Å particle size 70-230 mesh	391484
Silica gel Merck™ average Mw <500 particle size 63-200 µm Pore Size 70-230 mesh	403563
Silica gel Merck™ high purity particle size 63-200 µm particle size 70-230 mesh	403598
Silica gel Merck™ particle size 63-200 µm Pore Size 100 Å particle size 70-230 mesh	403601
Silica gel Merck™ with gypsum binder and fluorescent indicator TLC grade 7749	346446
Silica gel TLC grade 11678 average particle size 15 µm with gypsum binder and fluorescent indicator pore diameter 60 Å	403717
Silica gel TLC grade 11695 average particle size 15 µm with silica/alumina binder pore diameter 60 Å	403709
Silica gel Particle size 100-200 mesh (75-150 µm) Pore Size 25 Å (average pore diameter)	S4133
Silica gel particle size 28-200 mesh	214396
Silica gel Pore Size 30-60 mesh	214418
Silica gel Pore Size 6-12 mesh	214426
Silica gel Pore Size 3-9 mesh	214434
Silica gel particle size 6-16 mesh	214442
Silica gel particle size 14-20 mesh	214450
Silica gel particle size 100-200 mesh	214477
Silica gel Pore Size 150 Å particle size 60-200 mesh	243981
Silica gel particle size 8 mesh	249823
Silica gel Pore Size -200 mesh	270172
Silica gel Pore Size 60 Å pore volume 0.75 cm ³ /g particle size 200-400 mesh	288594
Silica gel Pore Size 60 Å pore volume 0.75 cm ³ /g particle size 130-270 mesh	288608
Silica gel Pore Size 60 Å pore volume 0.75 cm ³ /g particle size 70-230 mesh	288624
Silica gel particle size 60-200 mesh	343323
Silica gel Type II Particle size 1/8 in. (beads) Suitable for desiccation	S7500
Silica gel Type III Indicating For desiccation	S7625
Silica gel	S8394

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Liming Acid Soils in Tennessee

High Saucy, Jr., Associate Professor, Biosystems Engineering & Environmental Science
Originally written by John R. Jarek, Former Professor Plant and Soil Science

Soil test results indicate that approximately 50 percent of the cropland in Tennessee is too acid for optimum crop production. Because of this, determining the need for lime should be the first step in developing a sound crop fertilization program. Lime neutralizes excess soil acids and increases pH. If not limed as needed, soils continue to become more acid, reducing the soil's potential to produce healthy plants and profitable yields.

What is Soil Acidity?

Soil acidity refers to the level of acids present in soils. As acid levels increase, the pH of the soil decreases. While the pH scale ranges from 0-14, most Tennessee soils range in value from 4.5 to 7.5. Soils with pH values greater than 7.0 are alkaline or sweet, and those with values of less than 7.0 are acid or sour (Figure 1). As the soil pH decreases below 7.0, the amount of acidity rapidly increases. For example, a pH of 5.0 is 10 times more acid than 6.0 and 100 times more acid than pH 7.0.

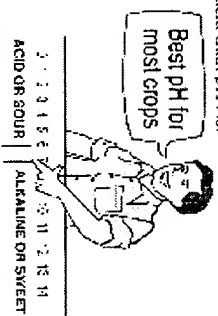
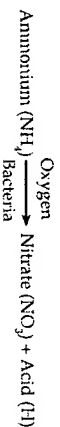


Figure 1. The pH Scale (Source: NCSA).

Causes of Soil Acidity

Several factors contribute to soil acidity. Acid levels increase as basic nutrients (calcium, magnesium, potassium) are replaced by hydrogen through soil erosion, leaching and crop removal. In addition, the use of acid-forming fertilizers greatly enhances acid levels. In particular, the conversion of ammonium (NH_4^+) nitrogen to nitrate (NO_3^-) nitrogen in the soil (nitrification) produces significant amounts of acid (H) as follows:



As a result, about 3 to 4 pounds of agricultural limestone are needed to correct the acidity formed from each pound of actual nitrogen applied to the soil from either ammonium nitrate, urea, UAN solutions or anhydrous ammonia.

Determining the Need for Lime (Water pH)

Soil pH is determined in the University of Tennessee Soil Testing Laboratory with the glass electrode using 10 grams of soil in 10 milliliters of deionized water. The value obtained is a measure of the degree of acid in the soil solution and is used to indicate whether or not lime is needed (Figure 2). It is the value referred to on soil test report forms as water pH.

Determining the Amount of Lime (Buffer pH or Buffer Value)

While water pH indicates the need for lime, buffer pH determines how much to apply. Buffer pH is a measure of the amount of acid held (adsorbed) by soil particles (clay, organic matter) and accounts for the acid that must be neutralized when lime is added. Buffer pH is reported as buffer value on all University of Tennessee soil test report forms.

The relation between water and buffer pH readings may be more easily understood by considering the relation between the fuel gauge and fuel tank in an automobile. The gauge indicates the relative need for fuel but says nothing about the gallons required to fill up. This depends on the size of the tank. For example, if the tank holds 20 gallons and the gauge indicates it to be one-fourth full, then 15 gallons of fuel would be required to refill the tank. If the tank's

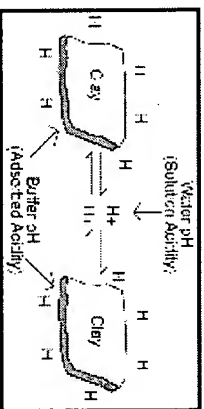


Figure 2. Relation between Water pH and Buffer pH.

capacity is 40 gallons, then 30 gallons of fuel would be necessary to refill the tank from one-fourth full.

When making lime recommendations, water pH is the "gauge" used to indicate the need for lime, while buffer pH is the "gauge" used to show how much lime should be applied to properly adjust the soil's pH, or "refill the tank." Clayey soils have more holding capacity or "larger tanks" than silty or sandy soils and require more lime to produce an equal amount of change in soil pH. Although water pH values may be similar for two or more soils, buffer pH values and recommended lime rates may differ greatly due to different clay levels and amounts of adsorbed acidity.

What Does Lime Do?

Applying lime to acid soils provides the following benefits:

1. Reduces amounts of soluble aluminum and manganese to non-toxic levels. As soil pH increases, the availability of manganese decreases, which prevents plants from taking up toxic amounts (Figure 3). Manganese toxicity becomes a major problem in many plants when the soil pH drops to near 5.0.
2. Supplies calcium, and if dolomitic limestone is used it supplies both calcium and magnesium, which are essential plant nutrients. Also, the availability of secondary and micronutrients is about optimum in the pH range of 6.1 to 6.5.
3. Increases the efficiency of N, P and K. For example, the efficiency of applied phosphate may be more than doubled when soil pH is increased from 5.0 to 6.1 because of less fixation or tie-up in the soil (Figure 4).
4. Enhances microorganism activity. Acid soils slow the growth and multiplication of certain microorganisms, which in turn reduces soil processes such as the release of nutrients from organic matter decomposition (mineralization) and nitrogen fixation in legumes.
5. Improves the effectiveness of certain herbicides (atrazine, etc.).
6. Increases yields and profits. University of Tennessee research indicates that three tons of limestone applied to soybean fields with soil pH values of 5.1 to 5.5 increased yields an average of 11 bushels per acre. In burley tobacco tests, yields were increased 1,024 pounds when four tons of limestone were applied to a soil with pH 4.4.

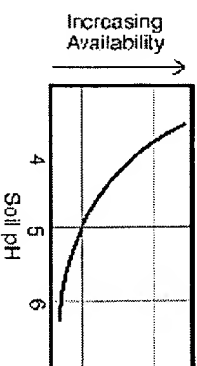


Figure 3. Influence of Soil pH on Manganese Availability.

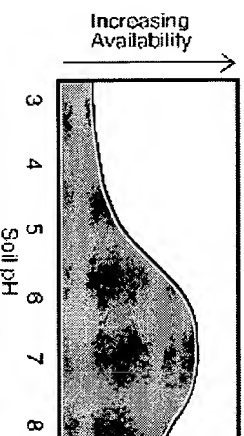


Figure 4. Influence of Soil pH on Phosphorus Availability.

When and How to Apply Lime

Although lime can be applied whenever soil, weather, crop and labor conditions permit, fall is an excellent time for spreading. Fields are usually dry, lime dealers are less rushed and growers are not occupied with spring planting.

Lime should be spread uniformly. Uneven distribution may present problems for several growing seasons since lime is not applied every year. The time interval between lime applications will vary depending upon soil type, weather conditions, cropping systems and fertilization (see Extension PB 1061).

Lime Sources

The primary function of a liming material is to correct acid soil conditions. Thus, materials that are easily spread and provide the greatest liming value at the least cost are the most desirable. The most common and economical liming material available in Tennessee is ground or agricultural limestone. Limestones containing both calcium and magnesium are DOLOMITIC. Those containing only calcium are

Attachment C 112

Calcium carbonate equivalent, fineness of grind and the relative neutralizing value are required to be indicated in a conspicuous manner on the label or tag of bagged materials and on the delivery slip or invoice for materials sold in bulk.

NOTE: Sieve or mesh size refers to the number of openings per linear inch of screen. For example, a 40-mesh sieve contains 40 openings per linear inch or 1,600 openings per square inch.

Relative Neutralizing Value (RNV)

The relative neutralizing value of a lining material is determined by calculating the total particle size efficiency and multiplying by the calcium carbonate equivalent as follows:

Percent Material in Each Size Range	Efficiency Factor	Particle Efficiency
5 (coarser than 10 mesh)	x .33	= 1.6
20 (10-40 mesh)	x .73	= 14.6
40 (40-60 mesh)	x .93	= 37.2
35 (finer than 60 mesh)	x 1.00	= 35.0
Total Particle Size Efficiency		= 88.4

If the above material had a calcium carbonate equivalent (CCE) of 90 percent, the RNV would be: 88.4 (particle size efficiency) X .90 (CCE) = 79

If the above material had a calcium carbonate equivalent (CCE) of 90 percent, the RNV would be: 88.4 (particle size efficiency) X .90 (CCE) = 79

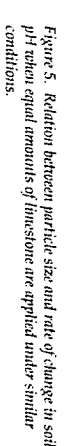
ground limestone will neutralize in the soil. Fineness of grind determines the rate limestone reacts with soil acids. Limestones coarser than 60-mesh will require from a few weeks to several months to produce significant changes in pH, while limestones 60-100 mesh will produce significant changes within two to three weeks when weather conditions are favorable and recommended amounts are applied (Figure 5). Limestones finer than 100 mesh produce results similar to 60-100 mesh materials when applied under similar conditions. Thus, small amounts of "extremely fine" limiting materials should not be substituted for recommended amounts of good quality ground lime-

stone. Also, extremely fine materials may be difficult to spread and handle.

The quality of agricultural limestone is

The importance of limestone quality
The quality of agricultural limestone is

The quality of agricultural limestone is determined by calcium carbonate equivalent and fineness of grind. The calcium carbonate equivalent determines how much acidity a given amount of ground limestone will neutralize in the soil. Fineness of grind determines the rate limestone reacts with soil acids. Limestones coarser than 60-mesh will require from a few weeks to several months to produce significant changes in pH, while limestones 60-100 mesh will produce significant changes within two to three weeks when weather conditions are favorable and recommended amounts are applied (Figure 5). Limestones finer than 100 mesh produce results similar to 60-100 mesh materials when applied under similar conditions. Thus, small amounts of "extremely fine" liming materials should not be substituted for recommended amounts of good quality ground limestone. Also, extremely fine materials may be difficult to spread and handle.



Agricultural limestones meeting state requirements usually contain adequate amounts of 60–100 mesh material.

Lime is very important to no-till crops, especially

in the top 2 inches of soil. If not neutralized, the acid will greatly reduce nutrient availability and herbicide activity, resulting in low fertilizer efficiency and poor weed control.

Where lime is needed, the same amount is recommended for no-till as for conventional practices. Research does not indicate any advantage to applying smaller amounts more frequently.

plant growth may be restricted unless the limestone is incorporated into the soil. Surface applications will require more time to neutralize acidity to greater depths than when incorporated into the soil.

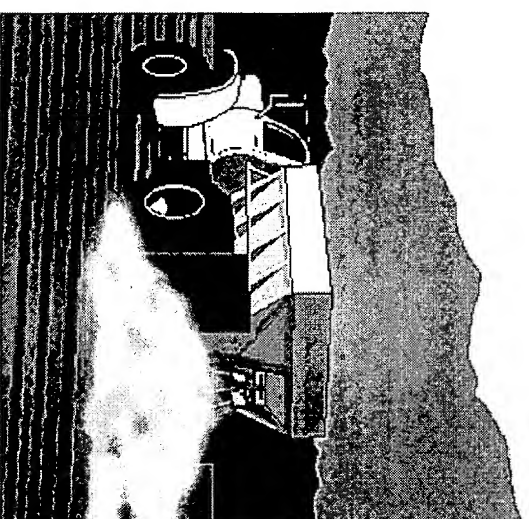
Soil samples for determining pH should be collected to a depth of 6 inches for both conventional and no-till row crops and pastures.

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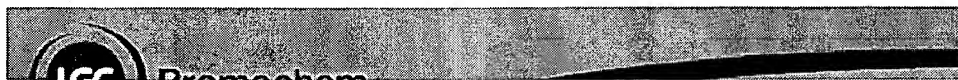
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PB1096

Liming Acid Soils in Tennessee



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Florisil PR for residue analysis. 60 - 100 mesh (150 - 250 um) SC-4182-B005 Size: 500g	More
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Florisil (Standard). 60 - 100 mesh (150 - 250 um) SC-4181-B005 Size: 500g	More
Florisil (Standard). 60 - 100 mesh (150 - 250 um) SC-4181-S010 Size: 10kg	More
ICN Alumina B - Super I (basic) (50 - 200 um) SC-4568-B005 Size: 500g	More
ICNAlumina B - Super I (50 - 200 um) SC-4569-B005 Size: 500g	More
ICNAlumina A - Super I (acid) (50 - 200 um) SC-4592-B005 Size: 500g	More
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Effect of Particle Size on Mixing Degree in Dispensation

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By using lactose colored with erythrocine, we examined the effect of particle size on mixing degree during the preparation of triturations with a mortar and pestle. We used powders with different distributions of particle sizes, i.e., powder that passed through 32-mesh but was trapped on a 42-mesh sieve (32/42-mesh powder), powder that passed through a 42-mesh sieve but was trapped on a 60-mesh sieve (42/60-mesh powder), powder that passed through a 60-mesh sieve but was trapped on a 100-mesh sieve (60/100-mesh powder), and powder that passes through a 100-mesh sieve (>100-mesh powder). The mixing degree of colored powder and non-colored powder whose distribution of particle sizes was the same as that of the colored powder was excellent. The coefficient of variation (CV) value of the mixing degree was 6.08% after 40 rotations when colored powder was mixed with non-colored powder that both passed through a 100-mesh sieve. The CV value of the mixing degree was low in the case of mixing of colored and non-colored powders with different particle size distributions. After mixing, about 50% of 42/60-mesh powder had become smaller particles, whereas the distribution of particle sizes was not influenced by the mixing of 60/100-mesh powder. It was suggested that the mixing degree is affected by distribution of particle sizes. It may be important to determine the mixing degrees for drugs with narrow therapeutic ranges.

Key words—dispensation; trituration; particle size; granules

INTRODUCTION

The degree of mixing in trituration is affected by many factors, including the physical property and mixing ratio of the principal agents and diluents, the mixing conditions and the kind of blender used. Many studies using a V-type blender have been performed to determine the effects of various factors on mixing degree.^{1–4)} However, there has been little investigation of the effects of factors on the degree of mixing using a mortar and pestle, which are frequently used in hospitals and general pharmacies. It has been reported that a satisfactory degree of mixing cannot be achieved by using a mortar and pestle when powders and granules are mixed.⁵⁾ It has also been reported that the uniform mixing was achieved by using a mortar and pestle after 60–80 rotations in the case of preparation of 5.0–30.0 g of powdered medicine when the gravity of the principal agent and that of diluents was similar.^{6–8)} In contrast to the fact that an excellent degree of mixing was achieved when powders with similar particle sizes were used, it has been

reported that the mixing degree of powders with different particle sizes was unsatisfactory. Although the 10th edition of the Japanese Guidelines for Dispensation indicates that medicines can be prepared by mixing powders and fine granules, there is no detailed information on the mixing degree of powders and fine granules.

In the present study, by using lactose colored with erythrocine, a food-coloring agent, we examined the effect of particle size on mixing degree during the preparation of triturations with a mortar and pestle, which are generally used for dispensation.

MATERIALS AND METHODS

Preparation of Lactose Lactose powder (20 g, lot number 099208, Yoshida Seiyaku Co., Ltd., Tokyo, Japan) was transferred to a glass mortar, and erythrocine (2 g, lot number GG41HH, Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan) dissolved in 5 ml of distilled water was added to the mortar and mixed well. After addition of the remaining lactose powder (78 g), the solution was mixed until it was homogeneous and was then passed through a 32-mesh dispensing sieve (screen size of 500 μ m). After dehydration

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at 60°C for 1 h using a circulating warm-air dehydrator, the resulting pellet was sieved through 100-mesh (screen size of 149 μm), 60-mesh (screen size of 250 μm), 42-mesh (screen size of 350 μm) and 32-mesh (screen size of 500 μm) dispensing sieves. We could thus obtain powders with different distributions of particle sizes, i.e., powder that passed through a 32-mesh sieve but was trapped on a 42-mesh sieve (32/42-mesh powder), powder that passed through a 42-mesh sieve but was trapped on a 60-mesh sieve (42/60-mesh powder), powder that passed through a 60-mesh sieve but was trapped on a 100-mesh sieve (60/100-mesh powder), and powder that passed through a 100 mesh sieve (>100 -mesh powder). Diluents were prepared from powdered lactose according to the method described above by using 5 ml of distilled water free of erythrocine.

Methods of Mixing A china mortar with an outer diameter of 10 cm and depth of 5.5 cm (Nik-katou Seiyaku, Tokyo, Japan) was used. The mortar was held and rotated by the left hand, and the pestle was rotated spirally in the direction opposite to that of the rotation of the mortar. For the mixing, 10 clockwise rotations followed by 10 anticlockwise rotations were repeated three times, the mortar thus being rotated 60 times. Rotation was performed at a constant rate (60 rotations/30 sec). In the present study, 10 g of colored lactose powders (>100 -mesh, 60/100- and 42/60-mesh powders), and the same amount of diluent lactose (>100 -, 60/100-, 42/60- and 32/42-mesh powders) were mixed in the mortar.

Determination of Particle Size After mixing, the distribution of particle sizes was determined by sieving the mixed powders through 32-, 42-, 60-, 80-, 100-, 150- and 200-mesh prescription sieves with screen sizes of 500, 350, 250, 177, 149, 105 and 74 μm , respectively.

Estimation of Mixing Degree After mixing, 1.0 g specimens were randomly taken from three portions of the mixed powders to determine the concentration of erythrocine. Each specimen was dissolved in distilled water to obtain a solution of 10 ml. The absorption at the wavelength of 524 nm was determined by using a spectrophotometer (UV-160, Shimadzu Co., Ltd., Kyoto, Japan).

Assuming that the contents of the major agents in the triturations were distributed according to the normal probability distribution, the coefficient of variation (CV) value was 6.08% under conditions in

which 90% of the powder fraction contained 100 ± 10 % of the expected amount of the major agent.⁹⁾ Therefore, the mixing degree was judged as excellent if the CV value of three determinations of erythrocine concentration in each preparation was less than 6.08 %.

RESULTS

Effect of Particle Size on Mixing Degree At first, we examined the mixing degrees of colored lactose having particle size of >100 -mesh with diluent lactose having particle sizes of >100 -, 60/100-, 42/60- and 32/42-mesh. The CV of the mixing degree became less than 6.08% after 40 rotations in the case of diluent lactose with particle size of >100 -mesh (Fig. 1). In contrast, 60 rotations were required to achieve a CV value of less than 6.08% in the case of diluent lactose with particle sizes of 60/100-, 42/60- and 32/42-mesh (Fig. 1).

It was also found that the CV value of the mixing degree of colored lactose having particle sizes of 60/100 and 42/60-mesh with diluent lactose having particle sizes of >100 -, 60/100-, 42/60- and 32/42-mesh became less than 6.08% after 60 rotations (Figs. 2 and 3).

Distribution of Particle Sizes after Mixing Distribution of particle sizes was examined after mixing colored lactose having particle size of 42/60-mesh with diluent lactose having particle size of 42/60-mesh. As shown in Table 1, after 100 rotations, 45% and 4% of the 42/60-mesh particles had become 60/100- and 100/150-mesh particles, respectively, due to the grinding/destruction of particles in the mortar. In contrast, only 12% of the 60/100-mesh particles had become 100/150-mesh particles after the mixing of 60/100-mesh particles (Table 2).

DISCUSSION

One of the most important factors that determine the degree of mixing in trituration is particle sizes of principal drugs and diluents. In the present study, we determined mixing degrees by using colored lactose. The CV value of mixing degree became less than 6.08 % after 40 rotations when colored lactose was mixed with diluent lactose whose particle sizes were the same as that of the colored lactose, except in the case of 42/60 mesh powder. Moreover, the CV value of mixing became less than 6.08% after 40 rotations when colored lactose with particle size of >100 -mesh was

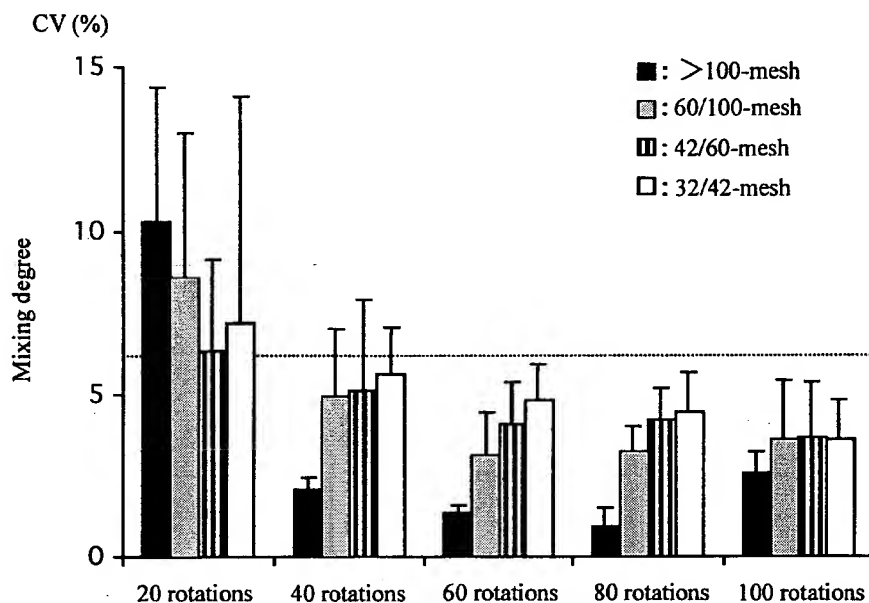


Fig. 1. Effect of Particle Size on Mixing Degree of >100-mesh Colored Lactose

Colored lactose having particle size of >100-mesh was mixed with the same amount of diluent lactose having particle sizes of >100-, 60/100-, 42/60- and 32/42-mesh. The mortar and pestle were rotated 20, 40, 60, 80 and 100 times. The results are given as CV value of the mixing degree. Each bar represents the mean \pm S.D. of three determinations.

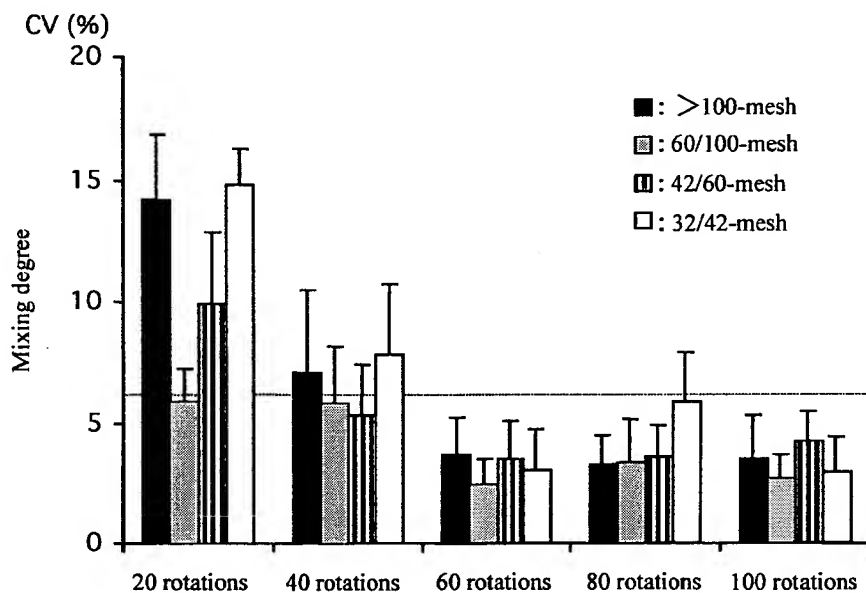


Fig. 2. Effect of Particle Size on Mixing Degree of 60/100-mesh Colored Lactose

Colored lactose having particle size of 60/100-mesh was mixed with the same amount of diluent lactose having particle sizes of >100-, 60/100-, 42/60- and 32/42-mesh. The mortar and pestle were rotated 20, 40, 60, 80 and 100 times. The results are given as CV of the mixing degree. Each bar represents the mean \pm S.D. of three determinations.

mixed with diluent lactose with particle size of >100-mesh, although we do not know the reason. It was also found that mixing degree was satisfactory when particle sizes of the colored and diluent lactose were the same than when they were different, especially for

small colored lactose samples.

In addition, the distribution of particle sizes was examined after mixing lactose powders whose particle sizes were 42/60- and 60/100-mesh. After 100 rotations, approximately 50% of the 42/60-mesh particles

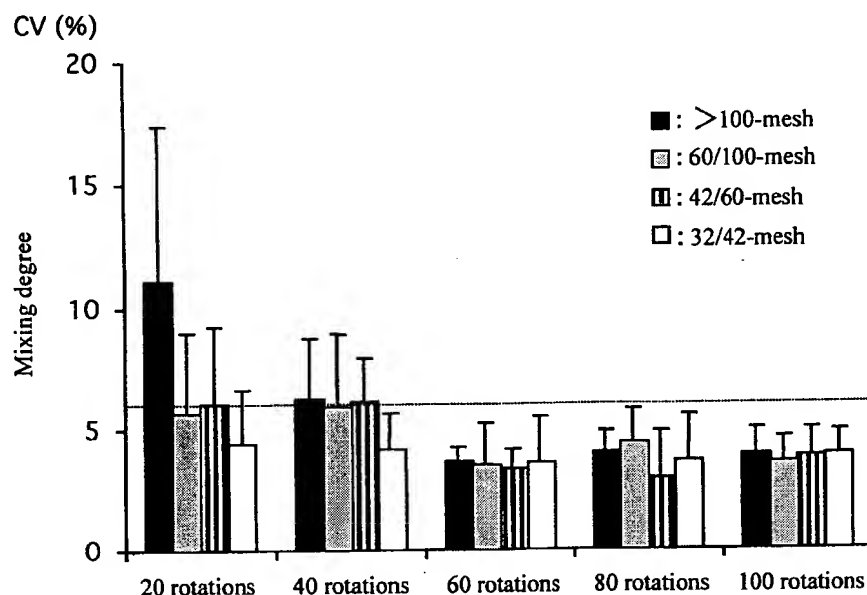


Fig. 3. Effect of Particle Size on Mixing Degree of 42/60-mesh Colored Lactose

Colored lactose having particle size of 42/60-mesh was mixed with the same amount of diluent lactose having particle sizes of >100-, 60/100-, 42/60- and 32/42-mesh. The mortar and pestle were rotated 20, 40, 60, 80 and 100 times. The results are given as CV of the mixing degree. Each bar represents the mean \pm S.D. of three determinations.

Table 1. Alterations in Particle Size Caused by Mixing of 42/60-Mesh Powders

Particle size	Mean \pm S.D. (%)
42/60-mesh	48.6 \pm 3.5
60/100-mesh	45.3 \pm 4.2
100/150-mesh	3.8 \pm 0.2
150/200-mesh	0.9 \pm 0.3
>200-mesh	1.4 \pm 0.5
Total	100

Powder with particle size of 42/60-mesh was mixed in a mortar and a pestle by 100 rotations. After mixing, particle size was determined using dispensing sieves. Each value is the mean \pm S.D. of three determinations.

Table 2. Alterations in Particle Size Caused by Mixing of 60/100-Mesh Powders

Particle size	Mean \pm S.D. (%)
60/100-mesh	85.3 \pm 3.2
100/150-mesh	12.3 \pm 1.8
150/200-mesh	0.8 \pm 0.2
>200-mesh	1.6 \pm 0.2
Total	100

Powders with particle size of 60/100-mesh was mixed in a mortar and a pestle by 100 rotations. After mixing, particle size was determined using dispensing sieves. Each value is the mean \pm S.D. of three determinations.

became smaller, whereas only 12% of the 60/100-mesh particles had become 100/150-mesh particles (Table 2). It was suggested that, in contrast to powders with small particle sizes, the mixing of large granules in the mortar results in an altered distribution of particle sizes. In preliminary experiments, we examined the distribution of particles by using a coated mortar, shaker and dispensing spoon. Forty five percent and 4% of the 42/60-mesh particles became 60/100- and 100/150-mesh particles, respectively, when a coated mortar and shaker were used. These results are consistent with the results obtained by using a regular mortar. In addition, 38% of the 42/60-mesh particles became 60/100-mesh particles after

mixing with a dispensing spoon. Taken together, the results indicate that alterations in the distribution of particle sizes occur after mixing using a regular or coated mortar, a shaker, and a dispensing spoon instead of a pestle.

Concerning the selection of diluents for preparation of triturations of granules, Aoki *et al.*⁷⁾ and Kobo *et al.*¹⁰⁾ reported that the diluent powder that passed through a 35-mesh sieve and powder that passed through a 50-mesh sieve but was trapped by 100-mesh sieve were suitable. Kozatani *et al.*⁹⁾ reported that the diluent powder that passed through a 36-mesh sieve but was trapped by 65-mesh sieve was suitable considering convenience in handling (such as

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mixing degree, repose angle and elusion coefficient). However, the distributions of particle sizes of powders and fine granules are different from each other, which is based on the definition of fine granules in the Japanese Pharmacopeia. Fine granules are defined in the 9th and 10th editions of the Japanese Pharmacopeia as particles for which less than 10% pass through a 200-mesh sieve. In contrast according to the Requirements for Antibiotic Products of Japan, 1993, fine granules are defined as particles for which more than 95% pass through a 32-mesh sieve. Consequently, the distribution of particle sizes of commercially available fine granules which consist of principal drugs is different from each other depending on the products. For example, approximately 10%, 18%, 37% and 34% of commercially available Aleve fine granules are 32/42-, 42/60-, 60/100- and >100-mesh particles, respectively, whereas approximately 62% of commercially available Serenace fine granules are trapped on a 48 mesh sieve. It is therefore possible that the degree of mixing of fine granules with powders is affected not only by the distribution of particle sizes but also by the degree of hardness of fine granules, since fine granules with a low degree of hardness may become smaller during mixing.

From these findings, it was suggested that the mixing degree is affected by the distribution of particle sizes but that 60 rotations may result in excellent mixing for particles of less than 32/42-mesh in size. For

preparation of triturations from fine granules with relatively large diameters, the degree of hardness of the fine granules may affect the mixing degree, since fine granules with a low degree of hardness may become smaller during mixing.

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